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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,976	02/13/2002	Robert J. Hariri	011307	1042

20583 7590 01/05/2006

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,976	HARIRI, ROBERT J.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments and responses filed 3/18/05 and 10/17/05 have been entered. Claims 1-23 have been canceled, claims 24-43 are newly submitted, and claim 24 has been amended. Claims 24-43 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in the responses would be addressed to the extent that they apply to current rejection.

Claim Objection

Claims 31-34 are objected to because a conjugation such as "that" or "which" should be inserted after "a placenta".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because claim 24 is incomplete. The claims are directed to a method comprising seeding stem cells from a mammalian placenta, however, it is unclear how such stem cells are obtained. Cells from a placenta perfusion

solution may contain a mixture of cells, the claim fails to set forth a positive step separating stem cells from the mixture, and thus the metes and bounds of the claim are unclear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

The amended claim 24 recites, "wherein said mammalian placenta has been treated to remove placental blood". Here, "treated to remove placenta blood" encompasses numerous means of placenta treatment, such as any one of draining, squeezing, flushing, perfusing, and for any length of period. Since residue umbilical cord blood could be present when the treatment is anything but perfusion for a lengthy period, the stem cells obtained from the treated placenta could be UCB or residual of UCB. Due to the ambiguity concerning which step(s) may be involved in the treatment, the source of the stem cells encompasses residues of cord blood or stem cells from a perfused placenta. Thus, the metes and bounds of the claims are uncertain.

In light of the specification, the treatment appears to be a combination of draining, flushing, and perfusion before the desired stem cells are obtained. The claims should be amended to precisely reflect the invention by adding a step of how the placenta is treated.

The claims are vague and indefinite because claim 24 requires seeding 'stem cells" in a tissue matrix, but since the "stem cells" encompass any type of stem cell,

such as mesenchymal stem cells, hematopoietic stem cells, and ES stem cells (see e.g. claim 29, ES cell markers), and most stem cells would be differentiated as soon as they are seeded, it is unclear what cell *component* and *status* the "seeded tissue matrix" comprises, e.g. ES cells only or a mixture of cells, or a specific type of differentiated cells, and thus the metes and bounds of the end product tissue matrix are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejections of Claims 1-12, 22, and 23 under the first paragraph of 35 U.S.C. 112 (written description and enablement) now apply to claims 24-43 for reasons of record and following.

Applicants argued that new claims do not encompass the use of embryonic stem cells, and the newly recited cell surface markers are supported by the specification.

In response, although applicants canceled claims reciting "embryonic stem cells", and the new claims define stem cells by cell surface markers such as those recited in claims 29-30, these markers are known to be present on ES cells (e.g. *Pera et al, Thomson et al*), thus the amended claims implicitly encompass ES cells.

Applicant then pointed to the support for such markers in page 28 of the specification for support of stem cell markers obtained from the perfused placenta.

In response, as indicated in the previous Office action (e.g page 6), the pointed teaching of the specification appears to be prophetic because in the section entitled

"isolation of placenta embryonic-like stem cells" (Specification, pages 43-44), applicants admitted, "no *attempts were made to further characterized these adherent cells" and "when subcultured, the placenta-derived embryonic-like stem cells ... adhered within hours, assumed characteristic fibroblastoid shape, and formed a growth pattern identical to the reference bone marrow-derived MSC*" (not ESC, emphasis added). In the result section that follows, the specification only contemplates using CD34 and CD38 markers, (which are not ES cell markers) and the specification is completely silent with regard to the outcome of CD34/CD38 cell sorting, and fails to teach what type of surface markers the cells obtained from the perfused placenta would bear. Accordingly, the specification fails to provide an enabling disclosure to support what is now claimed.

Applicant also argued that ABC-p is a placenta-specific marker citing Lorkowski as support. In response, *Lorkowski et al* (Pure Appl Chem 2002;74:2057-81) teach ABC-p, one of the ABCG subfamily of human ATP-binding cassette proteins, is present in placenta itself. *Lorkowski et al* fail to disclose that perfused placenta contains stem cells bearing ABC-p surface marker, and thus fail to support applicant's argument.

Applicant then argued that *Pera et al* does not discuss the identifying characteristics of placental stem cells.

In response, obtaining stem cells bearing ES cell surface markers is the instantly claimed invention, and was not known in the prior art. Thus, it is applicant's duty to teach that claimed markers are indeed present on cells obtained from the perfused placenta. Applicant has failed to do so, and thus fails to provide an enabling disclosure for what is claimed. Further, *Pera et al* (J Cell Sci 2000;113:5-10) was cited in support of

the position of the Office, i.e. even assuming arguendo that applicant has reduced to practice showing that stem cells obtained from the perfused placenta would have identified as SSEA3-, SSEA4-, OCT-4+, and ABC-p+, these markers alone cannot confirm the identity of ES cells; and the SSEA markers are present only in human but not mouse ES cells.

Claim 30 lists a group of cell surface markers present on stem cell surface, however, it is a common knowledge that majority of the recited markers belong to differentiated leukocytes, lymphocytes, or vascular cells, which are not stem cells. The specification fails to teach otherwise, and thus fails to support the full scope of the claims.

It is noted applicant fails to respond to the rejection due to lack of teaching regarding the culture conditions for various stem cells and how stem cells would grow and differentiate insight the tissue matrix, and thus the disclosure fails to teach how to use such matrix.

Accordingly, for reasons of record and those set forth supra, the rejection stands.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 24-27, 31, 35, 36, 41, 42 are rejected under 35 U.S.C. 102(e) as being anticipated by *Pykett et al* (USP 6,548,299).

Pykett et al teach a method of producing a three-dimensional matrix scaffold seeded with CD34+ hematopoietic progenitor cells, and the tissue matrix generated by the method; wherein the CD34+ cells may be collected from the cord blood (e.g. column 33, line 14), wherein the matrix tissue may be artificial or natural (e.g. column 9, line 61), and wherein the tissue lacking cells (decellularized), and preferably coated with biological substances such as fibronectins and glycosaminoglycans to promote cell adhesion, migration, and growth (e.g. column 10, lines 10-35). Accordingly, *Pykett et al* anticipate instant claims.

It is noted in this and following rejections, the cited reference applies to instant method claims because claim 24 as written encompasses conditions where residual cord blood remains in the placenta. If amending claim 24 to include draining and perfusion steps, the rejection on method claims would be obviated. However, the rejection on product claims would remain standing even if applicant amends claims as suggested. This is because the prior art product differs from the claimed product only by their method of manufacture, i.e. placental stem cells vs. peripheral blood CD34+ cells; or placental ES cells vs. ES cells from the inner cell mass of blastocyst. However, the claimed method of making the seeded tissue matrix would not distinguish them over the product taught by the prior art. Applicants are reminded that the court has ruled that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for

making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In the instant case, the CD34+ cells would be the same regardless how they are obtained, i.e. from a perfused placenta or from cord blood or adult peripheral blood.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 26-28, 35-40, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Pykett et al* (USP 6,548,299), in view of *Goldstein et al* (USP 5,899,936), and *Atala* (USP 6,753,181).

The teaching of *Pykett et al* was discussed *supra*. *Pykett et al* do not teach the ratio of the fibronectin to heparin, nor the details of how the stem cells are seeded on the matrices, nor the process of decellularization of a natural tissue/organ.

Goldstein et al and *Atala* supplemented *Pykett et al* by establishing that it was well known in the art the optimal ratio of the fibronectin to heparin for coating a bioprosthesis ranges from 0.1:1 to 10:1 (e.g. column 9, lines 7-17) and the process of decellularization of a natural tissue for making an implant. As to how the stem cells are

seeded, *Pykett et al* do not literally state how this was done. However, given the state of the art, the multiple means of seeding would have been common practice to one ordinary skilled in the art.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method taught by *Pykett et al, Goldstein et al*, and *Atala* by coating the matrices as taught by *Pykett et al* in an appropriate ratio of fibronectin to heparin as taught by *Goldstein et al* and decellularizing the matrix as taught by *Atala*, with a reasonable expectation of success. Given the state of the art, these limitations fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 102/103

The prior rejection of Claims 11 and 12 now applies to claims 41-43 under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Anderson et al* (USP 6,328,762) and as evidenced by *Thomson et al* (Science 1998;282:1145-7).

Anderson et al teach a tissue matrix (porous prosthetic implant) seeded with cells including stem cells from bone marrow (CD34+/-) and embryonic stem cells (e.g. claims 1 and 3), and a method of making such for tissue repair (e.g. abstract). Although *Anderson et al* do not describe the surface markers of the stem cells, the recited markers are well known in the art to stain or not stain for certain type of stem cells as evidenced by *Thomson et al* for example (paragraph bridging pages 1145-6). Thus,

Anderson et al anticipate or in the alternative as obvious over the instant claimed invention.

Applicant asserted that Anderson does not teach or suggest a tissue matrix comprising *placenta*-derived stem cells.

In response, as indicated previously and reiterated here, the claims are set forth as product-by-process claims, applicant is reminded that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, so long as the tissue matrix taught by *Anderson et al* meet structural limitation containing a matrix plus stem cells, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

The prior rejection of Claims 11 and 12 now applies to claims 41-43 under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Wu et al* (US 2003/0109042), for reasons of record, and following.

Applicant presented similar arguments as those in *Anderson et al*, which have been addressed supra, and will not be reiterated.

The prior rejection of Claims 11 and 12 now applies to claims 41-43 under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Buttery et al* (Tissue Eng 2001;7:89-99).

Applicant presented similar arguments as those in *Anderson et al*, which have been addressed supra, and will not be reiterated.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730.

The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

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Primary Examiner
Art Unit 1633

QJL
December 29, 2005